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Side effects in older patients: differences in incidence and management

Dr Battisti: Hello, my name is Nicolò Battisti, and I'm a medical oncologist working in the Breast Unit at The Royal Marsden Hospital of London in the UK. I am the President-Elect of the International Society of Geriatric Oncology, SIOG. Today, I will review the evidence available on the burden of systemic treatment complications in older individuals with breast cancer and discuss potential solutions to this key challenge. These are my disclosures. I will start with an overview on the complexity of using systemic anticancer treatment in older individuals, and then move on reviewing the available data on the safety for those with breast cancer. Finally, I will discuss the importance of integrating geriatric assessments in the routine care of older adults with cancer, with the aim to minimize the risk of toxicity. A key aspect to consider in the decision making for older adults with cancer is that they are heterogeneous, and we cannot easily make assumptions on the risk of adverse outcomes of anticancer treatments. As we age, we become increasingly diverse, due to the effect on our health of different comorbidities, the exposure to different health behaviours, levels of social support, and access to healthcare, and because we live in different geographical areas. In this context, fitness is a continuum. Fit patients have a longer life expectancy, minimal comorbidity burden, good functional status and organ reserve, more polypharmacy, and where the focus could still be survival. On the other hand, frail patients are those with a shorter life expectancy with increased burden of comorbidities, functional impairments, and polypharmacy, reduced organ function, and where the focus should be increasingly quality over quantity of life. However, a common challenge for clinicians is to identify who are those older patients that are seemingly frail, but actually able to tolerate and benefit from standard treatment approaches, and who are those that actually are seemingly fit, but prone to experience undue side effects and require an adaptive anticancer treatment plan. In this population, renal function is a key concern. The aging process correlates with a gradual decline in the glomerular filtration rate, a reduction in the renal mass, and drug clearance and the hyalinization of the renal vessels. The concurrent use of nonsteroidal anti-inflammatory drugs may cause further renal impairment, and this gradual decline may cause higher peak drug levels, and a more prolonged exposure to a number of anticancer treatment agents. In older patients, serum creatinine is no longer a reliable indicator of renal function due to muscle loss associated with the aging process, and creatinine clearance is a better measure of renal function, perhaps measured by Cockcroft-Gault formula, to inform the need for dose adjustments. Liver function is critical for the metabolism of a number of cytotoxic agents. Aging correlates with a gradual decline in the liver size, blood flow, first-pass metabolism, and drug clearance. However, this does not usually warrant any dose modifications. On the other hand, comorbidities, concurrent use of medications, or liver metastatic spread may require dose reductions. Bone marrow function is an additional concern in this population. Myelosuppression tends to be more frequent in older patients who experience a gradual decline in the stem cell reserve there and correlates with a higher risk of infections and hospitalizations and mortality compared

with younger counterparts receiving systemic anticancer treatments. And the ASCO guidelines recommend the use of primary G-CSF prophylaxis for patients receiving marrow suppressive treatments with a risk of neutropenia greater than 20%, while the NCCN guidelines mandate its use for older individuals receiving curative treatment. Anaemia may also have a significant impact on functional status in this population, and the use of erythropoietin-stimulating agents may also be considered for those not receiving curative treatment. Cardiac function changes associated with aging include a reduction in the cardiac output, heart rate modulation, myocardial hypertrophy, and conduction abnormalities. Along with an increasing burden of cardiovascular comorbidities, these changes may increase the risk for cardiotoxicity in older individuals. And this is a key concern for patients receiving, for example, anthracycline, trastuzumab, fluoropyrimidine, radiotherapy to the chest wall. Now, let's review some specific aspects on the safety of systemic anticancer treatment in older patients with breast cancer. For those with curable disease, retrospective data suggests that the risk for severe toxicity is higher in older versus younger patients. A SEER analysis conducted on 3,567 patients with early-stage breast cancer diagnosed in 2003 to 2007 reveals that hospitalizations were significantly more frequent for those age 65 plus compared with younger patients and ranging from 12% versus 6% on docetaxel and cyclophosphamide, and 23 versus 9% on a sequential combination with anthracyclines and taxanes. A retrospective SEER analysis that was conducted in the more than 40,000 patients aged 66 to 80 years diagnosed with Stage I to III breast cancer in 1992, 2002 with no history of congestive heart failure documented rates of congestive heart failure at five to 10 years. So, 19 and 38% respectively after use of anthracyclines, and 18 and 33% respectively after use of anthracycline-free chemotherapy. In this study, age, hypertension, diabetes, coronary artery disease, and trastuzumab use were obviously a significant predictor of cardiotoxicity. These studies outline the importance of selecting older patients suitable for chemotherapy in the context of the more limited benefits seen here and the importance of proactive cardiac management in order to minimize the risk of cardiotoxicity. Some investigators have evaluated the use of alternative chemotherapy regimens in the attempt to limit toxicities in older patients. The CALGB 49907 study showed a clearly different safety profile of capecitabine versus standard chemotherapy, CMF, or AC, in 633 patients with early-stage disease over the age of 65, and two drug-related deaths in those receiving capecitabine. The ELDA study also showed a different side effect profile in 302 patients aged 65 to 79 with average to high-risk early-stage disease with higher rates of side effects, and also worse effects on several quality-of-life domains on docetaxel. These two studies suggest that alternative chemotherapy regimen may not necessarily be safer in older patients with early-stage breast cancer. Quality of life is also a crucial endpoint for older patients in the context of the less pronounced benefits in survival outcomes on chemotherapy. And the Bridging The Age Gap study was a prospective observational study recruiting 3,416 patients over the age of 70 years diagnosed with breast cancer across the UK in 2013, 2018, and receiving more contemporary chemotherapy regimens. Among 1,520 patients with high-risk disease, including 1/4 of those receiving chemotherapy, at six months, chemotherapy had a significant detrimental impact on several EORTC quality of life C30 domains, including global health, physical role, social functioning, cognition, fatigue, nausea, vomiting, dyspnoea, appetite loss, diarrhoea, and constipation. But its impact was temporary and resolved in 18 to 24 months. What about the safety of anti-HER2 treatment in older patients with curable breast cancer? Here, we have data from a pooled analysis of the registration trials of trastuzumab, including more than 1,000 patients over the age of 60, and showing a 5% rate of cardiac events. Also, a retrospective SEER analysis of more than 2,000 women over the age of 66 diagnosed with Stage I to III breast cancer in 2005, 2009 reassuringly showed that 81% were able to complete the one-year course of trastuzumab, despite this was obviously influenced by age and comorbidities. These findings are even more reassuring in the context of the PERSEPHONE study, which indicates that shorter course of trastuzumab may not necessarily be detrimental in terms of efficacy compared with 12-months course, and in view of the fact that cardiotoxicity on anti-HER2 agents is reversible. The RESPECT study has recently compared outcomes for 275 patients aged 70 to 80 randomized with trastuzumab with, or without chemotherapy. Although the study failed to show non-inferiority of single agent trastuzumab in this patient population, it documented increased rates of side effects on those patients' receiving chemotherapy alongside trastuzumab. It did show

also similar rates of cardiotoxicity occurring in seven to 8% of patients, which were again, reversible with appropriate cardiac management, and the reversible effect on quality of life within 36 months as measured by the FACT-G questionnaire. For older patients with advanced ER-positive, HER2-negative breast cancer, CDK4/6 inhibitors have been evaluated in a pooled analysis of two randomized trials, including data on 456 patients age over 70. This analysis documented that the incidence of Grade 3 plus adverse events was 88% in those age, over the age of 75 versus 73% in those, the younger age group. Adverse events leading to dose reduction, or interruptions, occurred most frequently in those over the age of 75, 81 versus 71%, and similarly to those leading to discontinuation, 32 versus 12%, and older patients also experiencing decline in quality of life, however, regardless of the addition of CDK4/6 inhibitors. Subgroup analysis of BOLERO-2 on the right including only 121 patients aged 70 plus showed discontinuation due to toxicity in up to 17% of those receiving everolimus and on-treatment deaths due to adverse events in 7.7% of patients on everolimus, with significantly higher rates of side effects. And again, these data suggest the importance of patient selection also when it comes to considering adding targeted agent to endocrine therapy in this population. Data on the safety of anti-HER2 agents for older patients in the palliative setting at the right from the registHER observational study, more than 1,000 patients with advanced HER2-positive disease including 209 patients over the age of 65. Consistently with the data from the curative setting, the incidence of Grade 3 plus left ventricular dysfunction and congestive heart failure increased with increasing age up to 4.8 and 3.2% respectively above the age of 75. Since the CLEOPATRA study included only a tiny proportion of older patients, and docetaxel might be challenging to deliver in this population, EORTC 75111 study investigated the use of metronomic cyclophosphamide alongside dual anti-HER2, this versus with dual antibodies alone in patients over the age of 70. In this study, rates of [Audio Not Clear] suppression were obviously higher in those receiving chemotherapy, but there were no episodes for the neutropenia. However, diarrhoea occurred in 71% of those receiving chemotherapy combination versus 59% of those receiving, dual anti-HER2 antibodies alone, which may be a challenge. The management of systemic treatment toxicity should not change in older versus younger patients. However, I will now discuss a few aspects on the role of geriatric assessment as a solution to address the increased risk of systemic treatment toxicities in this population. Comprehensive geriatric assessment is a multidisciplinary diagnostic and therapeutic process evaluating and addressing domains related to the well-being of older individuals, such as comorbidities, function, cognition, nutritional status, mood, fatigue, polypharmacy, and geriatric syndromes. And several studies have suggested that CGA provides a wide range of benefits in this population. It can predict complications of anticancer treatments and functional decline, estimate survival, aid treatment decisions, identify problems that might be neglected by routine assessments, and improve the mental health, well-being, and pain control of these patients. Crucially, three Phase III randomized clinical trials presented at 2020 ASCO annual meeting have documented a positive impact on CGA on other endpoints, including toxicities, quality of life, unplanned hospitalization for older patients receiving systemic anticancer treatments. On the left, the GAP70 cluster randomized study enrolled 718 patients aged 70 plus with incurable Stage III to IV cancer, and more than one impaired geriatric assessment domain, other than polypharmacy, due to start a new line of systemic anticancer treatment in 41 community oncology practices in the States with recommendations sent to the primary oncologist based on geriatric assessments versus usual care. The study documented a statistically significant reduction in the rate of severe toxicity in the experimental arm compared with the standard arm, 50 versus 71%, along with a reduction in non-hematological toxicity, 31 versus 51% that might be explained by a more frequent upfront dose reduction used in cycle one in the experimental arm, 48 versus 35%, although there was no impact on survival at six months. The GAIN study has a similar design and was conducted at large academic centre in California. Here, 600 patients aged 65 plus with solid tumours of any stage and commencing a new line of chemotherapy were randomized to usual care plus the geriatric assessment-driven interventions versus standard care following a baseline geriatric assessment, which was reviewed by a multidisciplinary study team and reviewed by the treating oncologist. The study again documented a statistically significant reduction in the rates of Grade 3 plus chemotherapy-related toxicity, 50 versus 60%. INTEGERATE study enrolled 154 patients age over 70 with solid tumours of diffuse large B-

cell lymphoma due to receive systemic treatments were randomized to an integrated onco-geriatric approach versus usual care in three general hospitals in Melbourne, Australia. And it did document a 39% reduction in the emergency presentations, a 41% reduction in unplanned hospital admissions, a 24% reduction in the risk of unplanned hospital overnight stay, along with lower early treatment discontinuation, 32 versus 53%, but no differences in treatment reductions, escalations, and delays. A key aspect of CGA is the ability to predict risk of severe toxicities in older patients receiving chemotherapy. For example, the Cancer and Aging Research Group Breast Cancer CARG-BC Score designed by Arti Hurria, and Allison Magnuson combines breast cancer stage, planned use of anthracyclines and chemotherapy durations, haemoglobin levels, liver function, number of falls within the previous six months, functional status, social support to determine the risk of Grade 3 plus adverse events on chemotherapy for patients aged 70 plus with early stage breast cancer. As you can see here, the score outperformed prognostic performance status in chemotherapy toxicity prediction in the validation analysis. And additional chemotherapy prediction tools are available also for patients with advanced disease. In conclusion, an increasing amount of evidence suggest that in order to minimize the risk of toxicity on systemic anticancer treatment for older patient with breast cancer, it is crucial to consider their overall health alongside tumour-specific aspects. Similarly to what happened over the last two decades when we moved away from simply driving anticancer treatment decision based on histology, grade, and stage, and we are now looking at a number of biomarkers, we should do the same when looking at our patients' characteristics, and move beyond simply considering chronological age and performance status, but embed geriatric assessment in the routine care of our patients while considering life expectancy, organ function, comorbidities, functional status, social support, and potential effects on quality of life and patient preferences in order to achieve what we can really call precision oncology. We have included these suggestions in the EUSOMA, SIOG recommendations that have updated recently and published in "Lancet Oncology" that I would highlight as a useful resource to guide clinical practice here, alongside a few additional resources, such as the SIOG website, the Cancer and Aging Research Group website, the website of Moffitt Cancer Center Senior Adult Oncology Program, the "Journal of Geriatric Oncology," and finally, a few hashtags that you can use to interact and network with the geriatric oncology community on social media. Thank you very much for your attention, and goodbye for now.